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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,410	12/14/2001	Peggy J. Farnham	960296.97401	1459

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,410	FARNHAM ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/15/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6,7,9,11-13 and 16-18* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,11-13 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 September 2005 has been entered.

Claims 6, 7 and 9 are withdrawn for reason of record from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 2-4, 6, 7, 9, 11-13, and 16-18 are pending. Claims 2-4, 11, 12, 13, and 16-18 are examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections, Withdrawn

The objection of claims 11-13 is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

The rejection of claims 12 and 13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the amendment.

Claims 2-4, 11-13, and new claims 16-18 **are rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-4, 11-13, and new claims 16-18 are interpreted as drawn to a genus of nucleic acid molecules with various degrees of variations, i.e. 80–95 % identity to the coding sequence of SEQ ID NO: 1, and 3, and hybridizing molecules under the recited conditions to the coding sequence of SEQ ID NO: 1, and 3, wherein the genus encode a protein overexpressed in liver tumor cells relative to regenerating normal cells.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

Applicant argues that the specification provides structural description by teaching the mouse sequence (SEQ ID NO:1), and the human mouse sequence (SEQ ID NO:3) which are at least 85 % identical over the coding sequences, and the proteins translated from those two cDNAs (i.e. SEQ ID NO:1, and 3) are 91% identical. Applicant also argues that the instant application at paragraph 00029 teach an existence of variants of

SEQ ID NO: 1 and 3 due to allele polymorphism, interspecies differences, and the present application makes clear that the invention encompasses these variants.

These arguments have been fully considered but found unpersuasive. As the prosecution history indicates, the Office has not rejected SEQ ID NO: 1, and 3. Therefore, comparing SEQ ID NOs 1 and 3 to each other is not commensurate in scope of claims. As for applicant's argument that allelic variants and interspecies variants are encompassed, the court has dealt with similar issue in deciding University of California v. Eli Lilly, 43 USPQ2d 1398. The court stated that the specification from University of California failed the written description requirement of the patent law, because the University of California specification only provides the protein sequence of human insulin, and rat cDNA encoding the rat insulin, not the human cDNA itself. The court clearly stated that the specification fails to provide an adequate written description for the naturally occurring nucleic acid species (i.e. a human cDNA encoding a human insulin), even in the case that the entire protein sequence that should be encoded by the corresponding cDNA was disclosed in the specification. The court stated providing a method of obtaining the cDNA by means of a constructive example, although might be providing an enabling disclosure, nevertheless does not provide an adequate written description. The court in deciding another DNA case in Fiers v. Revel (CAFA) 25 USPQ 2d 1601 stated that "a mere wish or plan for obtaining the claimed invention" does not satisfy written description requirement. Therefore, the genus encompassed in the claims, i.e. o allele polymorphism, interspecies differences.

As for the argument with the new limitation "a protein overexpressed in liver tumor cells relative to regenerating normal liver cells", the specification does not teach which core structure is necessary for the function. The specification does not disclose if any protein overexpression is correlated with any in vivo tumor growth. The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. See enablement rejection for further detail on this matter. Graveel et al., Oncogene, 2001, vol. 20, pages 2704-2712, IDS filed on 2/21/02, at Table 2 (page 2708) teach that the instant SEQ ID NO: 1 encodes a putative protein. In other words, the in vivo existence of the protein has not been established, let alone overexpression of it. In summary, there is no correlation between the structure of the genus of the claimed nucleic acids and the overexpression of the protein. Thus, the instantly claimed partial structure in the form of the percent similarities along with the recited hybridization conditions, and the functional characteristics recited in claim 2 have no correlations.

As stated above, a review of the full content of the specification indicates the specification does not discloses a representative number of species" or "disclosure or relevant identifying characteristics, such as structure or other physical and/or chemical properties", and/or describing functional characteristics coupled with a known or disclosed correlation between function and structure. The functional characteristic recited is uncoupled with the structure of the claimed genus. There is no correlation between the chemical structure of the claimed genus and the recited function. Therefore the recited functional language describing the claimed genera does not

adequately describe the common feature of claimed generic nucleic acid molecule. In addition, the specification does not give any guidance as to which domains or residues of SEQ ID NO: 1 or 3 are critical for the recited expression.

The specification must provide sufficient distinguishing identifying characteristics of the genus other than the partial structures in order to provide an adequate written description. The specification fails to provide functional characteristics, and/or structure/function correlation for the claimed genus. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid molecules, given that the specification has only described SEQ ID NO: 1 and 3. Therefore, only isolated nucleic acid comprising SEQ ID NO: 1 and 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

In addition, claim 2, step (v) says the hybridizing molecules (i.e. a complement) to a coding sequence also encode proteins. The specification does not teach any complement encoding a protein, let alone being overexpressed in liver tumor.

As for claim 11, the claimed genus of the hybridizing molecules nor the reference sequence have any function associated with the genus.

The **new matter rejection of record** is also maintained because of the previously added limitation "80 % identity to the coding sequence of SEQ ID NO: 1, or 3" in the base claims 2, and 11 is a new matter.

Applicant argues cites Moba B. V. vs. DiamondAutomation Inc., 325 F.3d 1306 (Fed. Cir. 2003), Inverness Medical Switzerland GmbH v. Acon Laboratories Inc. (D. Mass., No. 03-1 1323, 4/29/05), and argues that the court faced the issue of whether the written description requirement is satisfied for a claim directed at an immunoassay test device without a casing, which was not expressly described in the specification. The court stated that the question is not whether the specification expressly described a test device operable without a casing, but whether a skilled person in the art would understand from the specification that the applicant had invented a device without casing. Having found that a person skilled in the art would understand from the specification that the casing not necessary for the device to operate, the court held that the written description requirement is satisfied. As in Inverness, a skilled artisan would understands that applicant had invented a nucleic acid that is at least 80% identical to the coding sequence of SEQ ID NO: 1 or 3.

These arguments have been fully considered but found unpersuasive. The casing in applicant's argument is not necessary for the claimed device to operate. However, the instant coding sequence is not the case. Therefore, the court decisions relating to the casing does not seem to be applicable to the instant case. Question of whether one skilled in the art would have known that applicant had possession of the subgenus that cause new matter rejection in the last Office action, applicant does not have a single species that is 80% identical to the coding sequence of SEQ ID NO: 1 or 3, other than SEQ ID NO: 1 or 3, which were not subject to written description rejection. Especially applicant does not provide any domain or core structure that must be

conserved in order to have the recited function of encoding a protein overexpressed. Therefore, one of skill would not understand that applicant had possession of the claimed genus at the time the application was filed.

Claims 2-4, 11-13, and new claims 16-18 **are rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 1, 3, and nucleic acids encoding SEQ ID NO: 2, and 4, does not reasonably provide enablement for any other nucleic acid molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is □undue□ include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The scope of enablement rejection is made because the nature of the invention is interpreted as drawn a genus of nucleic acid molecules with certain degree of similarity to SEQ ID NO: 1 or 3, wherein the genus encodes a protein overexpressed in liver tumor.

Applicant argues that the amended claims are limited to hybridizing molecules to the coding sequence of the nucleic acids encoding protein overexpressed in tumors, and applicant is not required to enable more than one use.

These arguments have been fully considered but found unpersuasive.

The specification does not disclose if the protein overexpression encoded is correlated with any in vivo tumor growth. The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. See enablement rejection for further detail on this matter. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from

patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. In addition, Bussenmakers et al., Cancer Res. 1999 Dec 1;59 :5975-90 teach that not all

cancer-specific mRNA overexpression is a human gene without necessarily encoding any protein. Graveel et al., Oncogene, 2001, vol. 20, pages 2704-2712, IDS filed on 2/21/02, at Table 2 (page 2708) teach that the instant SEQ ID NO: 1 encodes a putative protein. In other words, the in vivo existence of the protein has not been established, let alone overexpression of it. In summary, there is no correlation between the structure of the genus of the claimed nucleic acids and the overexpression of the protein. Thus, the instantly claimed partial structure in the form of the percent similarities along with the recited hybridization conditions, and the functional characteristics recited in claim 2 have no correlations.

The enablement requirement requires how to make and use claimed product. As discussed above, the instant specification does not teach how to make the allelic or interspecies variant. As stated in the previous Office action, the specification at pages 8 and 9 teaches that SEQ ID NO: 1 is over-expressed in mouse LIVER TUMOR (hepatocellular carcinoma) and SEQ ID NO: 3 is also over-expressed in human LIVER TUMOR. However, the specification does not teach which other nucleic acid molecules other than SEQ ID NO: 1 and 3 are expressed in LIVER TUMOR.

The relative level of skill in making nucleic acid molecules that are over-expressed in liver tumor is low. Graveel et al., (IDS, 2001, Oncogene, vol. 20, pages 2704-2712) teach the current state of how one of skill isolates a nucleic acid that is over-expressed in liver tumor. It requires screening a large quantity of clinical samples, namely liver tissue from patients with liver tumor, followed by isolating mRNA species that are differentially and preferentially expressed in liver tumor. In other words, one

skilled in art has to determine what other mRNA species are differentially or preferentially expressed in liver tumor. Which other similar sequences could be used as liver tumor or cancer marker is still unpredictable until said sequences are experimentally determined by screening a large quantity of appropriate clinical samples.

The breadth of the claimed invention is broad including many unknown species.

The level of predictability, which nucleic acid molecule resembling the coding sequence of the instant SEQ ID NO: 1 will be expressed in liver tumor is low as shown by Graveel et al (2001). It requires experimental determination if they ever exist. The amount of direction or guidance by the inventor how to use the full scope of claimed nucleic acid molecule with the recited partial structural element is limited. There is not adequate guidance or direction to allow the person of ordinary skill in the art to make the claimed nucleic acids in a manner commensurate in scope with the claims. The quantity of experimentation needed to make the invention is large. In order to make the full scope of the invention, one skilled in the art has to screen a large quantity of clinical samples from liver or pancreatic tissue of patients having liver tumor followed by sequence the nucleic acid composition. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves. How to make the claimed nucleic acids that are 80 % identical to the coding sequence of SEQ ID NO:1, or 3 encodes a protein expressed in LIVER TUMOR requires undue experimentation because one has to screen Limiting the scope to the enabled species, i.e. SEQ ID NO: 1 and 3 would obviate this scope of enablement rejection.

Claim Rejections - 35 USC § 102

The rejection of claims 2-4, 11, and 13 under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al., (1996, Genome Research, vol. 6, pages 791-806) is withdrawn because the amended claims are no longer anticipated.

Claims 11-13 **remain rejected** under 35 U.S.C. 102(b) as being anticipated by Wu et al., (April 12, 1996, Biochim Biophys Acta. Vol. 1315, issue no. 3, pages 169-75).

Claims 11-13 are drawn to kit comprising an oligonucleotide that hybridizes to the coding sequence of SEQ ID NO: 1 and 3, wherein the kit also contains liver tumor sample as a positive control and non-tumor liver samples as a negative control.

Applicant argues that Wu reference does not anticipate the amended claims because the scope is limited to the hybridizing nucleotide to the coding sequence of SEQ ID NO: 1.

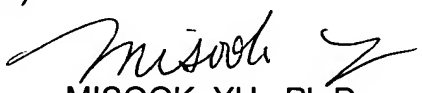
These argument has been fully considered but found unpersuasive because the primer at page 170, left column, has a primer with "CGGAC" which would hybridizes to "gcctg", which spans nucleotide #115 to 119 under the recited conditions if the concentration of the primers are high enough. Note the melting temperature is 45.8 °C under Ix SSC (.15 mM NaCl) according to IDT Oligoanalyzer 3.0 downloaded from world wide web idtdna.com on 2/14/2006. Johnson et al., Journal of Neurochemistry, Volume 64 Page 967-8 only March 1995 is attached to show that 1X SSC is .15 mM NaCl, note page 968, right column.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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